REMARKS

Rejection of claims under 35 U.S.C. 112:

Claims 5, 16, and 17 have been rejected under 35 U.S.C. 112. Claim 5 has been amended to remove the time period reference that lacked antecedent basis. Claims 16 and 17 have been amended to replace the word "and" with the word "or" as recommended by the Office Action. Claim 17 has been further amended remove the limitation which lacked antecedent basis.

Applicants have either amended the claims to obviate the rejections. Applicants respectfully request that the §112 rejections be removed.

Double Patenting:

Claims 8-15 have been rejected as being unpatentable over claims 1 and 3-14 of U.S. Patent No. 6,379,966. Applicants will file a terminal disclaimer upon allowance of the claims.

Claims 1-7 have been provisionally rejected as being unpatentable over claims 7,9,11 and 12 of copending Application No. 09/391,260. Applicants will file a terminal disclaimer upon allowance of the claims.

Claims 1-7, 17 and 18 have been provisionally rejected as being unpatentable over claims 19, 20 and 22 of copending Application No. 09/447,966. Applicants will file a terminal disclaimer upon allowance of the claims.

Claims 1-7 have been provisionally rejected as being unpatentable over claims 1-15 and 37 39 of copending Application No. 09/707,000. Applicants will file a terminal disclaimer upon allowance of the claims.

Rejection of claims under 35 U.S.C. 102:

Claims 1-5, 7-13, 15 and 17 have been rejected under §102 as being anticipated by US 5,328,470 and US 5,698,531 (Nabel et al. and Nabel et al.). The office action states that Nabel et al taught delivery of a polynucleotide to an extravascular cell by increasing permeability of blood vessel using increased pressure against the blood vessel walls. Applicants respectfully disagree and believe that Nabel et al, in '470 and in '531, provided no teaching or guidance on delivery of nucleic acid to cells outside of a blood vessel; i.e., non-vascular cells.

Nabel, in '470 and in '531, twice mentions the use of high pressure. The first instance occurs in column 8, starting at line 36 (of '470): "Using a different catheter design (see FIG. 2), a different protocol for instillation can also be used. This second approach involves the use of a single balloon means (2) catheter with multiple port means (3) which allow for high pressure delivery of the retrovirus into partially denuded arterial segments. The vessel surface is prepared as described above and defective vector is introduced using similar adhesive molecules. In this instance, the use of a high pressure delivery system serves to optimize the interaction of vectors with cells in adjacent vascular tissue."

The second reference to high pressure occurs in column 8, starting at line 53 (of '470): "It is also possible to transform cells within an organ or tissue. Direct transformation of organ or tissue cells may be accomplished by one of two methods. In a first method a high pressure transfection is used. The high pressure will cause the vector to migrate through the blood vessel walls into the surrounding tissue. In a second method, injection into a capillary bed, optionally after injury to allow leaking, gives rise to direct infection of the surrounding tissues. ¶ The time required for the instillation of the vectors or cells will depend on the particular aspect of the invention being employed. Thus, for instilling cells or vectors in a blood vessel a suitable time would be from 0.01 to 12 hrs, preferably 0.1 to 6 hrs, most preferably 0.2 to 2 hrs. Alternatively for high pressure instillation of vectors or cells, shorter times might be preferred."

The first reference to high pressure clearly indicates that high pressure results in delivery to partially denuded arterial segments. The second reference indicates that high pressure causes the vector (presumably a viral vector according to the preceding paragraph) to migrate through the vessel wall. No distinction is made between high pressure which results in arterial wall transfection and high pressure which results in migration of the virus out of the vessel. While the Nabel '470 specification provides evidence of delivery to cells in a vessel wall, no support for delivery to extravascular cells is made in '470. Nor is evidence of delivery to extravascular cells made in subsequent patents or publications by the inventors of '470. Also, no method is put forth for causing migration of a virus through a vessel wall.

The following quotation was taken from a review article written by E. Nabel where she cited other Nabel et al. published articles: Circulation, 91:541-548 (1995), pg 543, col. 2, last paragraph: "Several observations concerning the delivery of recombinant genes and patterns of gene expression can be drawn from these studies. Infusion of vector into normal arteries with an intact endothelium results in transfection of intimal cells (primarily endothelial cells). Injury to the vessel and/or application of pressure to the vector infusate results in delivery of DNA transmurally and gene expression in the media." Applicants point to the specific limitations in scope that the author places on the extent to the types of cells that are transfected using the '531 processes.

Both Gary and Elizabeth Nabel are authors of the following statement in 1997, six years after their '531 application was filed: "Although gene delivery to the pulmonary circulation has both experimental and therapeutic potential, the delivery methods, distribution of transgene, and subsequent inflammatory response have been poorly characterized to date ... This technique should prove useful for investigations requiring over expression of novel genes in the pulmonary artery wall, and could ultimately be used to develop gene-based therapies for pulmonary vascular diseases." (Am J Respir Cell Mol Biol 1997 Jun;16(6):640-9).

As further indication that the method taught by Nabel fails to achieve delivery to extravascular parenchymal cells, Applicants draw attention to statements made by E. Nabel in an amendment filed on Nov. 22, 1993 in the file history of US Patent No. 5,698,531. On page 5 of the amendment, Nabel states "Site-specific instillation of the various genes is achieved by... introducing the DNA or RNA sequences via a balloon catheter which isolates these sequences to a specific region of the arterial wall... By transforming the cells in the blood artery, expressed therapeutic gene products are steadily profused downstream into the involved tissue. The invention relies on recombinant gene expression within transduced vascular cells in a localized arterial segment... ." On page 12 of the amendment, Nabel states, "These results are significant because they demonstrate that the direct injection of

recombinant DNA in vivo results not only in the transformation of the arterial wall at the injection site, but also in expression of the desired gene product..." and "... human patients were treated by direct gene transfer... This gene was expressed in tissues localized to the instillation site... ." These statements clearly indicate that the transformed cells are restricted not only to cells of the arterial wall, but to cells of a very localized section of the arterial wall–a section delimited by the balloon catheters.

In addition, as indicated, the method taught by Nabel provides for delivery of a therapeutic protein to a downstream tissue only by expression and secretion of the protein from upstream arterial cells. The method taught by Nabel provides no direction on delivery to cells other than endothelial and smooth muscle cells located in a very small, defined region of a blood vessel. DNA is not directly delivered to parenchymal cells. Applicants recognize that general background statements made in Nabel '531 suggest that DNA may be delivered to parenchymal cells. However, no evidence of such delivery is provided. Nor is there any specific teaching of a method in which an extravascular cell is the intended delivery target.

It is clear from the '531 inventor's statements (after the filing date) that vessel wall transfection using balloon injury is their area of interest. To this date, Applicants have not found any references by the Nabels that describe delivery and expression beyond vessel walls. The Applicants therefore believe that it can not be determined from the teaching of Nabel–in '470, '531, or subsequent publications–how to achieve delivery to any cell other than a localized vessel wall cell. The Federal Circuit has repeatedly held that the specification must teach the method in a way that would allow a person having ordinary skill in the art to use the method without 'undue experimentation', in re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The mere mention of a possible method is not considered teaching the method. In Genentech Inc. V. Nordisk A/A, 42 USPQ2d 1001 (CAFC, 3/13/97) the specification describes three or four applications for which cleavable fusion expression is well-suited. The Federal Circuit ruled that such statements do not describe specific material or any reaction conditions and therefore do not teach. The Court stated on page 1005 that tossing out the mere germ of an idea does not constitute a teaching. The '470 and '531 specification contain lists of potential occurrences and future possibilities but do not teach how to deliver a polymer complex to an extravascular cell.

Conversely, the invention taught by the Applicants provides a significantly improved nucleic acid delivery procedure in which nucleic acid can be delivered to extravascular cells directly. Applicants' process is not limited to delivery of nucleic acid encoding secreted proteins in order to achieve a therapeutic effect on extravascular parenchymal cells.

In addition, Applicants' process does not require a catheter, does not involve Nabel-like "injury" to the vessel wall, and the cells need not be located in the immediate vicinity of the instillation point of the nucleic acid. All of these are significant advances over Nabel et al. delivery methods.

The office action also states that claim 8 is anticipated by Nabel et al '531 because the polynucleotide-liposome complex taught by Nabel et al '531 is known to have a less negative zeta potential than the polynucleotide alone. Applicants believe that the complex of claim 8 is clearly distinct from a polynucleotide-liposome complex that is less negative than the polynucleotide alone because the complex is further modified by adding another compound which increases the negative charge of the polynucleotide-liposome complex.

Rejection of claims under 35 U.S.C. 103:

Claims 1-18 have been rejected under 35 U.S.C. 103(a) as being unpatentable over '470 and '531 in view of Hwang '558. For the reasons stated above in response to claim rejections under 35 U.S.C. 102, Applicants believe that '470 and '531 do not provide guidance that enables one skilled in the art to deliver a polynucleotide using increased pressure to a cell other than a vascular cell. Furthermore, the liposomes used by Hwang are small unilamellar vesicles that have a neutral charge, are composed of neutral lipids, and have a circulation time of 5 hours or more. Because of the high negative charge of nucleic acid, cationic lipids must be used to interact with nucleic acid. Cationic lipids do not form liposomes that have extended stability in serum or prolonged circulation times. Therefore, Applicants believe that because the liposomes used by Hwang are incompatible the nucleic acid delivery, it can not have been obvious to one skilled in the art to combine the teaching of Hwang for delivery of neutral liposomes to the liver by tail vain injection with the teaching of Nabel.

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-18 should be allowable.

Respectfully submitted,

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